

# Clinical Pharmacology and Toxicology of Dichloroacetate

Peter W. Stacpoole,<sup>1,2</sup> George N. Henderson,<sup>1</sup> Zimeng Yan,<sup>1</sup> and Margaret O. James<sup>3</sup>

<sup>1</sup>Department of Medicine, <sup>2</sup>Department of Biochemistry and Molecular Biology, College of Medicine, <sup>3</sup>Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, Florida

Dichloroacetate (DCA) is a xenobiotic of interest to both environmental toxicologists and clinicians. The chemical is a product of water chlorination and of the metabolism of various drugs and industrial chemicals. Its accumulation in groundwater and at certain Superfund sites is considered a potential health hazard. However, concern about DCA toxicity is predicated mainly on data obtained in inbred rodent strains administered DCA at doses thousands of times higher than those to which humans are usually exposed. In these animals, chronic administration of DCA induces hepatotoxicity and neoplasia. Ironically, the DCA doses used in animal toxicology experiments are very similar to those used clinically for the chronic or acute treatment of several acquired or hereditary metabolic or cardiovascular diseases. As a medicinal, DCA is generally well tolerated and stimulates the activity of the mitochondrial pyruvate dehydrogenase enzyme complex, resulting in increased oxidation of glucose and lactate and an amelioration of lactic acidosis. By this mechanism, the drug may also enhance cellular energy metabolism. DCA is dehalogenated *in vivo* to monochloroacetate and glyoxylate, from which it can be further catabolized to glycolate, glycine, oxalate, and carbon dioxide. It remains to be determined whether important differences in its metabolism and toxicology exist in humans between environmentally and clinically relevant doses. — *Environ Health Perspect* 106(Suppl 4):989–994 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-4/989-994stacpoole/abstract.html>

Key words: dichloroacetate, pyruvate dehydrogenase, chlorination, drug metabolism, glyoxylate, oxalate, neuropathy

## Introduction

Dichloroacetate (DCA) is one of a host of organohalides to which humans have long been chronically exposed. Environmental sources of DCA include chlorinated drinking water (1–3) and groundwater contamination by certain industrial solvents and other chlorinated precursors (4). DCA is also a metabolite in the biotransformation of several pharmaceuticals (5,6) and has been administered orally and parenterally for decades as an investigational drug for the treatment of numerous cardiovascular and metabolic disorders. Collectively, these

data indicate that daily human exposure to DCA encompasses a 10,000-fold concentration range, from approximately 4 µg/kg consumed in finished drinking water to approximately 50 mg/kg administered for therapeutic purposes.

A comparative assessment of the kinetics, metabolism, and toxicology of DCA in animals and humans has recently been summarized (7). Here we focus on the clinical pharmacology and safety of this unusual chemical, based in large part on investigations conducted in healthy volunteers

or in children and adults with various congenital or acquired metabolic diseases for which DCA is administered acutely or chronically as a drug.

## Pharmacodynamics

From a medicinal standpoint, a principal site of action of DCA is the pyruvate dehydrogenase (PDH) enzyme complex (PDC) located in the mitochondrial inner membrane. PDC catalyzes the reversible decarboxylation of pyruvate to acetyl coenzyme A (CoA), which is the rate-limiting step in the aerobic oxidation of glucose, pyruvate, and lactate in animal cells (Figure 1).

PDC undergoes rapid posttranslational modulation in activity, due in part to reversible phosphorylation. PDC kinase phosphorylates and inactivates PDC, whereas PDC phosphatase dephosphorylates the complex and restores catalytic activity. DCA inhibits the kinase, thereby locking PDC in its unphosphorylated active form. This effect occurs within minutes of oral or parenteral administration of DCA, which is rapidly transported across cell membranes via the monocarboxylate carrier (8) and is concentrated in mitochondria (5).

The ability of mitochondria to oxidize substrates and produce adenosine triphosphate (ATP) by oxidative phosphorylation is integral to normal homeostasis and to the ability of cells to survive in the face of impending energy failure. Experimental and clinical investigations with DCA suggest that the drug primes the tricarboxylic acid (TCA) cycle with acetyl groups and the respiratory chain with electrons donated by the reducing equivalents generated by the PDC- and TCA-cycle-catalyzed reactions, thereby promoting ATP synthesis (Figure 2) (5). The ability of DCA to stimulate the efficient conversion of substrate fuel (glucose or lactate) into energy provides a biochemical rationale for its utility in ameliorating acquired or congenital causes of lactic acidosis and other pathologic conditions associated with mitochondrial energy failure. Indeed, studies by many investigators have firmly established DCA as the most potent lactate-lowering agent ever used clinically and a potential treatment for myocardial ischemia or failure (9).

## Kinetics and Metabolism

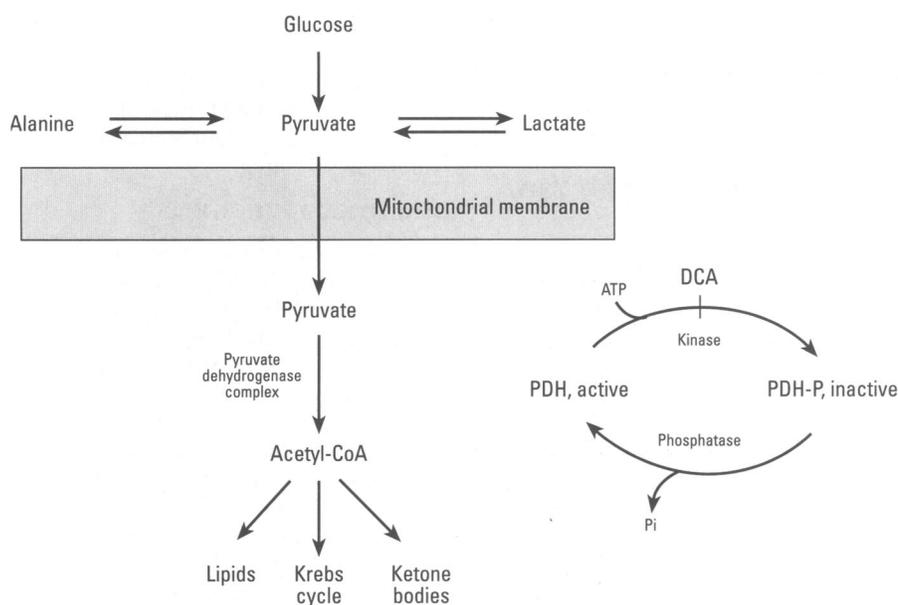
Dichloroacetate is rapidly and virtually completely absorbed following oral dosing and about 20% is bound to human plasma proteins (10). In all species examined to

This paper is based on a presentation at the Symposium on the Superfund Basic Research Program: A Decade of Improving Health through Multi-Disciplinary Research held 23–26 February 1997 in Chapel Hill, North Carolina. Manuscript received at *EHP* 11 December 1997; accepted 21 April 1998.

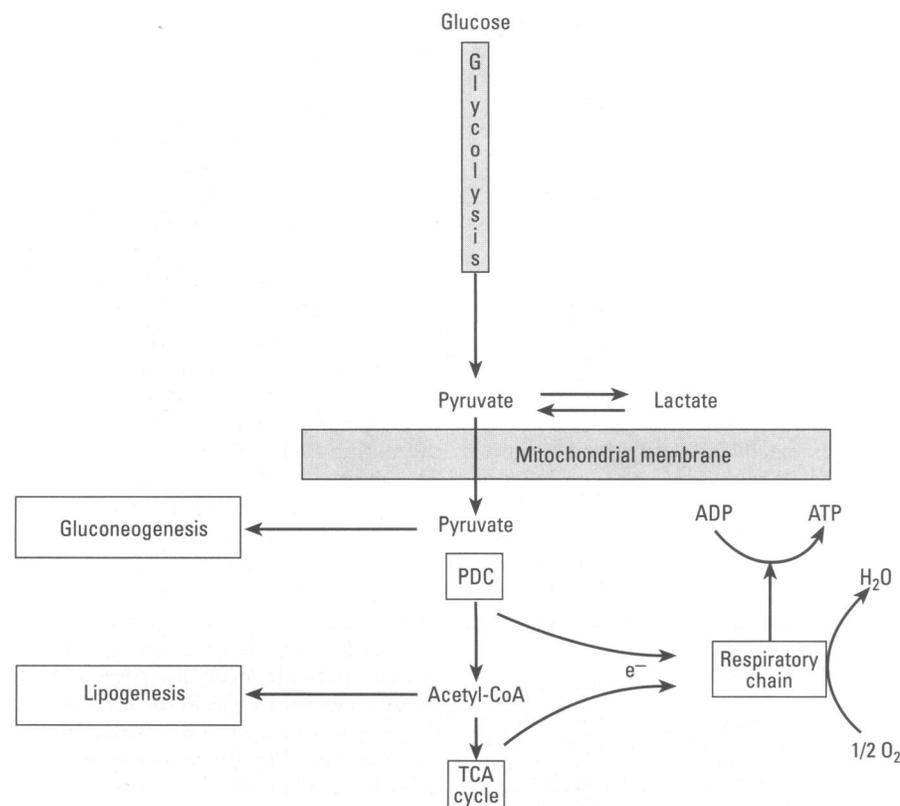
This work was supported by grants ESO R017355, ESO P427375, and RR00082 from the National Institutes of Health. We thank F. Clark and V. Busch for editorial assistance.

Address correspondence to P.W. Stacpoole, PO Box 100226, University of Florida, 1600 Southwest Archer Road, Gainesville, FL 32610-0226. Telephone: (352) 392-2321. Fax: (352) 846-0990. E-mail: stacpool@gcr.c.ufl.edu

Abbreviations used: ATP, adenosine triphosphate; AUC, area under the plasma concentration curve; CH, chloral hydrate; CLA, congenital lactic acidosis;  $C_{max}$ , peak plasma concentration;  $C_{min}$ , minimum plasma concentration; CoA, coenzyme A; DCA, dichloroacetate; MCA, monochloroacetate; PDC, pyruvate dehydrogenase complex; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid.



**Figure 1.** Site of action of dichloroacetate. DCA inhibits the mitochondrial enzyme PDH kinase, thereby maintaining the PDH complex in its unphosphorylated catalytically active state and facilitating the aerobic oxidation of glucose.



**Figure 2.** Cellular metabolism of glucose and oxidative phosphorylation. By activating the PDC, DCA primes the TCA cycle with acetyl-CoA molecules derived from glucose. Reducing equivalents, in the form of reduced nicotinic adenine dinucleotide and reduced flavin adenine dinucleotide from the PDC and TCA, reactions donate electrons ( $e^-$ ) to the respiratory chain, leading to the reduction of oxygen to water and to the synthesis of ATP from adenosine diphosphate. Reproduced from Stacpoole et al. (13) with permission of the BMJ Publishing Group.

date, the first dose is cleared from plasma more rapidly than subsequent doses, although the mechanism for this effect is unknown. Also unclear is the quantitative importance of its varied metabolic routes and the influence of repeat administration thereon. Glyoxylate is an intermediate in DCA metabolism, and oxalate and  $CO_2$  are terminal end products. Neither glyoxylate nor oxalate stimulate PDC activity (5). However, because the actions of DCA in humans often persist several days after its clearance from plasma (5), it is possible that other reactive intermediates of DCA accumulate intracellularly at active sites and bind covalently to target proteins, or that DCA (or a metabolite) induces enzymes responsible for its pharmacodynamic effects.

DCA is extensively metabolized in rodents and humans, with little of the dose excreted unchanged (7). Although most drug metabolism studies have been prompted by concern about DCA as a potential environmental pollutant, nearly all experiments to date have administered doses to animals and humans in the therapeutic (i.e., milligram per kilogram) rather than the environmental (microgram per kilogram) range. Thus, it remains unknown whether the kinetics and metabolism of the compound differ at these extremes of human exposure.

### Adults

To investigate the *in vivo* metabolism of DCA in humans, we recently developed and validated a gas chromatography/mass spectrometry technique that simultaneously measures DCA and its metabolites monochloroacetate (MCA), glyoxylate, glycolate, and oxalate in human plasma (11). Following administration of [ $^{13}C_{1,2}$ ] DCA, the drug and its metabolites are derivatized to their methyl esters by reacting them with a 12%  $BF_3$ -methanol mixture. Lactate, a glycolytic end product that is frequently measured following DCA administration, can also be quantitated by this technique.

Healthy men and women 18 to 65 years of age receive sequential oral DCA doses of 25 mg/kg and 250, 25, and 2.5  $\mu$ g/kg daily for 5 consecutive days. The highest and lowest doses are also administered intravenously for 5 days. The order of oral versus intravenous administration for these doses is randomized. This spectrum of DCA doses allows us to compare the kinetics and metabolism in each gender during exposure to both environmentally and clinically relevant levels, i.e., over a 10,000-fold concentration range. A 2- to

3-month washout period occurs between studies, as our previous investigations (10,12) demonstrated that an initial DCA dose in healthy subjects increases the plasma  $t_{1/2}$  of a subsequent dose, even after a washout period of several weeks.

These ongoing studies were initiated using the 25 mg/kg dose for two practical reasons: first, to optimize our chances of identifying metabolites of [ $^{13}\text{C}$ ]DCA in plasma and urine, and second, to generate comparative data with our pediatric investigations early on. Table 1 summarizes the mean data analyzed to date from 18 subjects who received oral or intravenous DCA for 5 days. On days 1 and 5, detailed kinetic investigations were performed over 24-hr sample collection periods. Subjects received a 1:1 mixture of [ $^{13}\text{C}$ ] and [ $^{12}\text{C}$ ]DCA on these days and [ $^{12}\text{C}$ ]DCA on days 2 to 4.

In general, the kinetic profile of a 25-mg/kg dose appears to be independent of gender and administration. Peak plasma concentration ( $C_{\text{max}}$ ) did not change appreciably between genders or between the first and fifth intravenous doses, but

the  $C_{\text{max}}$  after the final oral dose ( $158 \pm 99$   $\mu\text{g}/\text{ml}$ ) was 68% greater than after the initial dose ( $94 \pm 45$   $\mu\text{g}/\text{l}$ ). We speculate this difference may reflect faster gastrointestinal absorption of DCA upon repeated administration, perhaps by induction of some transport mechanism. Chronic dosing in all subject categories led to a striking increase in  $t_{1/2}$ , and this was associated with a fall in plasma clearance and an increase in the area under the plasma concentration curve (AUC). Urinary DCA accounts for approximately 1 to 2% of the administered initial dose and approximately 3 to 5% of the fifth dose, based on 24-hr urine collections.

Figure 3 shows representative plasma concentrations of [ $^{13}\text{C}$ ]DCA (Figure 3A) and its metabolites (Figure 3B) after a 25-mg/kg dose infused over 10 min. Note the rapid rise and fall of MCA, which in some subjects may reach levels up to 10% of the DCA  $C_{\text{max}}$  on a molar basis. Glyoxylate and oxalate concentrations, although measurable, are usually lower than MCA during the first 4 hr after dosing.

## Children

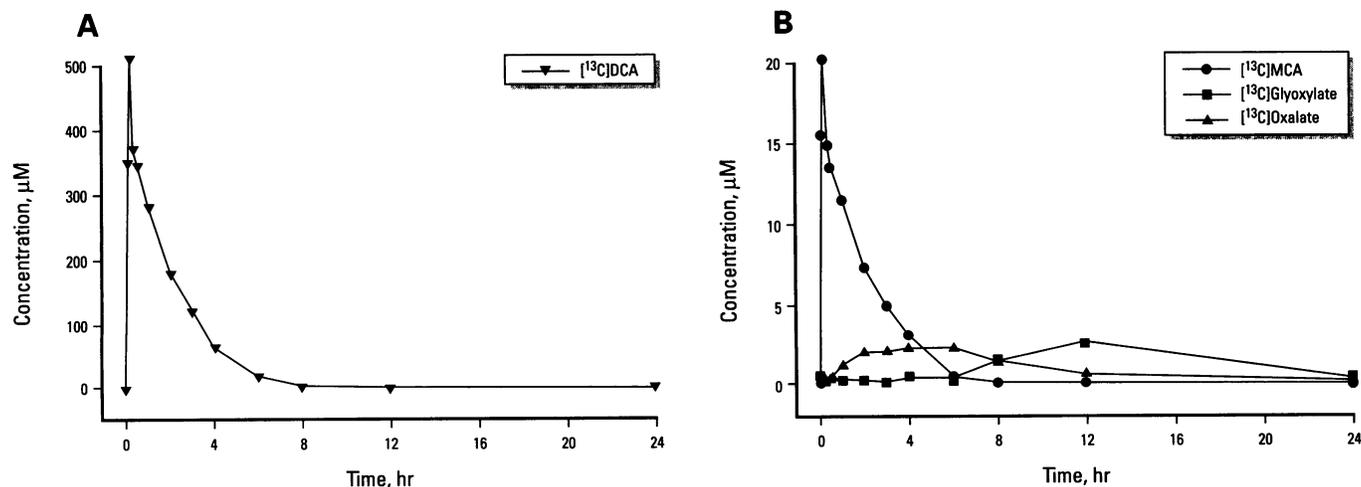
The term congenital lactic acidosis (CLA) refers to a group of rare inborn errors of metabolism variably characterized by progressive neuromuscular deterioration and accumulation of lactate and hydrogen ions in blood, urine, or cerebrospinal fluid, frequently resulting in early death. The incidence and prevalence in the United States are approximately 250 and 1000 cases, respectively. Most identifiable causes involve inherited or spontaneous mutations in PDC or in one or more enzymes of the respiratory chain. More than 50 CLA infants and children worldwide have received oral or intravenous DCA (13) in open-label investigations. Drug dose and treatment duration varied widely. Twelve patients received DCA for at least 1 year and three received it for at least 5 years. Thus, the cumulative DCA treatment experience in CLA infants and children is greater than 41 patient-years.

A controlled clinical trial is now being conducted to test the central hypotheses that DCA is safe and improves the quality

**Table 1.** Dichloroacetate kinetics in healthy adults.

Category	n	$C_{\text{max}}$ , $\mu\text{g}/\text{ml}$		AUC, hr $\mu\text{g}/\text{min}$		Clearance, ml/min/kg		Half-life, hr	
		Day 1	Day 5	Day 1	Day 5	Day 1	Day 5	Day 1	Day 5
Entire group	28	129 $\pm$ 73	163 $\pm$ 84	229 $\pm$ 138	1334 $\pm$ 763	0.160 $\pm$ 0.10	0.025 $\pm$ 0.01	1.07 $\pm$ 0.43	9.10 $\pm$ 8.46
Female	14	132 $\pm$ 76	146 $\pm$ 64	255 $\pm$ 144	1351 $\pm$ 833	0.130 $\pm$ 0.06	0.024 $\pm$ 0.01	1.15 $\pm$ 0.40	9.49 $\pm$ 7.15
Male	14	126 $\pm$ 70	180 $\pm$ 98	203 $\pm$ 127	1298 $\pm$ 684	0.190 $\pm$ 0.13	0.026 $\pm$ 0.02	0.98 $\pm$ 0.45	8.71 $\pm$ 9.57
Treatment 1	18	136 $\pm$ 82	154 $\pm$ 71	237 $\pm$ 145	1318 $\pm$ 871	0.160 $\pm$ 0.11	0.026 $\pm$ 0.01	1.03 $\pm$ 0.40	8.56 $\pm$ 7.10
Treatment 2	10	117 $\pm$ 53	181 $\pm$ 102	216 $\pm$ 125	1336 $\pm$ 515	0.162 $\pm$ 0.09	0.024 $\pm$ 0.01	1.12 $\pm$ 0.49	10.05 $\pm$ 10.39
Intravenous	14	165 $\pm$ 79	168 $\pm$ 66	263 $\pm$ 151	1374 $\pm$ 876	0.150 $\pm$ 0.12	0.026 $\pm$ 0.02	1.19 $\pm$ 0.48	7.73 $\pm$ 4.94
Oral	14	94 $\pm$ 45	158 $\pm$ 99	196 $\pm$ 114	1275 $\pm$ 626	0.170 $\pm$ 0.08	0.025 $\pm$ 0.01	0.94 $\pm$ 0.34	10.47 $\pm$ 10.72

n, number of kinetic studies. <sup>a</sup>Data are means  $\pm$  SD.



**Figure 3.** Plasma concentrations of (A) [ $^{13}\text{C}$ ]dichloroacetate and (B) its metabolites after a 25-mg/kg infusion of [ $^{13}\text{C}$ ]DCA. Note the rapid appearance and disappearance in plasma of MCA following the administration of DCA.

of life and metabolic status of infants and children with CLA due to PDC or respiratory chain defects. Safety is determined principally by finding that chronic DCA does not cause hepatocellular, peripheral nerve, ocular, or renal toxicity (all of which have been reported in dosed animals) or toxicity related to other organ systems. Quality of life is quantified by such key biologic indices of drug efficacy as improvement in neurologic, neurobehavioral, and physical function and by reduction in the frequency and severity of hospitalizations due to acid-base decompensation or other CLA-related complications. Biologic markers of cellular energy metabolism that are measured include blood and cerebrospinal fluid lactate (which should fall because of DCA's mechanism of action) and height (which should increase because of the amelioration of the metabolic acidosis). Improvement in these markers should track closely with quality of life indices. In addition, the kinetics and metabolism of [ $^{13}\text{C}$ ] and [ $^{12}\text{C}$ ]DCA are examined prospectively and are interpreted

in light of the dynamic and toxicologic effects of the compound.

[ $^{13}\text{C}$ ]DCA kinetics are performed at entry with a 2.5- $\mu\text{g/g}$  dose of compound and 3 to 4 times with 12.5 mg/kg DCA during the initial 24-month period. The dose of 2.5  $\mu\text{g/kg}$  is chosen because it is too small to exert any important pharmacodynamic effect and because it reflects the amount expected to be consumed by environmental exposure. Thus, the study affords the opportunity to examine repeatedly the kinetics and metabolism of DCA during both environmental and clinical dose phases.

Table 2 and Figure 4 show representative data on DCA kinetics and metabolism in CLA patients. The patient in Table 2 received 12.5 mg/kg every 12 hr by mouth.  $C_{\text{max}}$  levels were usually achieved 1 hr after the dose and minimum plasma levels were obtained at the dosing interval. In a second patient, Figure 4 illustrates the expected change in plasma drug clearance. In sharp contrast to our prior studies in adults with acquired causes of lactic acidosis (14,15) or in healthy volunteers, both Table 2 and Figure 4 demonstrate that repeated dosing in children appears to lead to progressive increases in  $C_{\text{max}}$ . Figure 5 illustrates the plasma metabolism of an oral 12.5 mg/kg dose of DCA (1:1 isotope ratio) in a child with CLA. As with healthy adults, MCA is an immediate and short-lived product, whereas glyoxylate and oxalate have more protracted time courses.

In the CLA study, children are administered 50 mg/kg chloral hydrate (CH) by

mouth to induce short-term conscious sedation for various neurologic tests. During the course of our DCA kinetic experiments, we noted the presence of a major interfering substance in some plasma samples. We determined this substance was CH and, in the course of these investigations, discovered that DCA is a major metabolite of CH in humans (6). We also found that CH and DCA may compete for similar routes of biotransformation. This conclusion is based in part on the observation that prior administration of CH delays the plasma clearance of DCA.

The discovery that humans catabolize CH to DCA has important implications for the kinetics, dynamics, and toxicology of both compounds. Both are found in microgram per liter quantities in municipal drinking water and are considered by the U.S. Environmental Protection Agency to be environmental hazards. The interesting possibilities are raised that the mental status changes induced by CH and (in some individuals) DCA may have a common mechanism and that CH may alter intermediary metabolism in the host by virtue of its conversion to DCA.

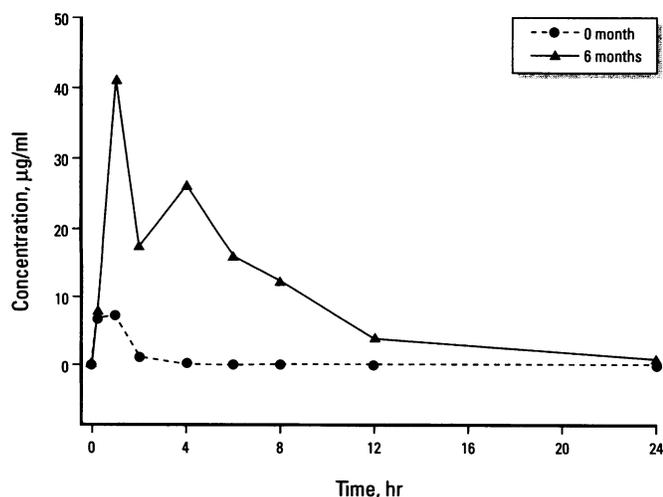
### Toxicology

A valid assessment of the human risk of DCA is confounded by the fact that most animal toxicology has focused on its chronic administration to subprimates, usually at doses nearer to those used clinically than to levels anticipated from environmental exposure of the chemical, its precursors,

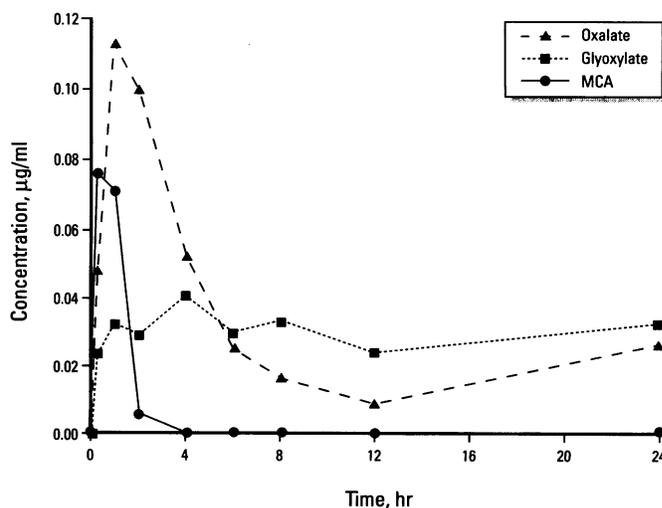
**Table 2.** Plasma dichloroacetate kinetics in a child with congenital lactic acidosis.

Treatment time	Half-life, hr	$C_{\text{max}}$ , $\mu\text{g/ml}$	$C_{\text{min}}$ , $\mu\text{g/ml}$
Day 1, first dose	0.74	39	0
Day 5	2.35	51	0
Month 3	6.06	115	46
Month 9	7.47	154	38

$C_{\text{min}}$ , minimum plasma concentration.



**Figure 4.** Change in dichloroacetate kinetics after 6 months in a patient with congenital lactic acidosis. Note the increase in the peak plasma concentration and the decrease in plasma clearance in DCA following chronic oral administration.



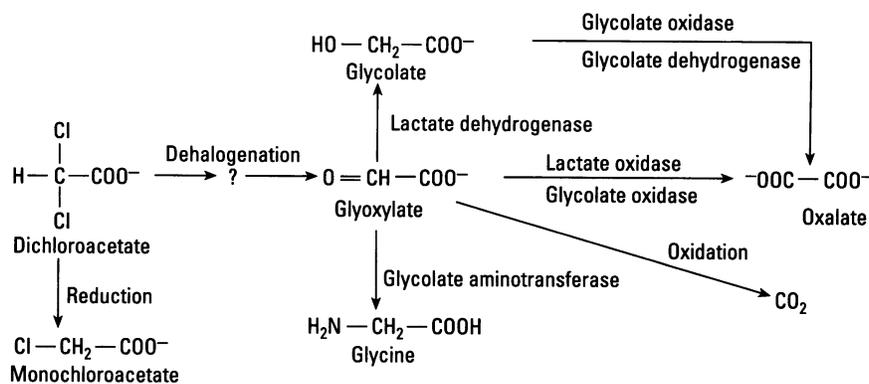
**Figure 5.** DCA metabolites for [ $^{13}\text{C}$ ]dichloroacetate in a patient with congenital lactic acidosis: first DCA treatment. The plasma concentration of MCA peaks and decays rapidly following a single dose of DCA.

or its catabolites. The animal toxicology of DCA has recently been reviewed (7). In brief, the liver, kidney, nervous system, testes, and eye are potential target organs of chronic DCA toxicity. Studies in rats and mice have shown that DCA can induce hepatocellular injury, hypertrophy, hyperplasia, adenomas, and carcinomas after chronic oral exposure to levels similar to those administered clinically (7).

To date, evidence of DCA toxicity in humans is limited and is primarily restricted to the nervous system and the liver. Approximately 50% of healthy adults receiving single or repeated oral or intravenous doses of 25 or 50 mg/kg DCA exhibit anxiolytic or sedative effects. These symptoms usually occur within 60 min of drug administration and may last several hours (16,17). Mild drowsiness or diminished anxiety have also been observed in a few patients with diabetes mellitus (18) or lactic acidosis (14) treated briefly with DCA. These central nervous system changes occur unpredictably and without obvious predilection for any particular gender, race, age group, or route of drug administration.

A reversible peripheral neuropathy occurred after several months of daily oral 50 to 100 mg/kg DCA treatment in two children with CLA due to PDC deficiency or a respiratory chain defect (7). Return to pretreatment neurologic states was achieved, both clinically and by nerve conduction velocity testing, within 6 months of discontinuing DCA. In the patient with PDC deficiency, resolution of the neuropathy led to retreatment with DCA at doses of 10 to 25 mg/kg/day, which has been continued for over 2 years without evidence of peripheral neuropathy.

Mild (-2-fold) asymptomatic elevation of serum transaminases has been noted in at least two children with CLA (17) and may reflect hepatocellular damage. Both patients received 25 to 75 mg/kg DCA daily for several months. Reduction in the highest dose



**Figure 6.** Biotransformation of dichloroacetate. This scheme postulates the existence of two principal *in vivo* routes of dichloroacetate catabolism: by reduction to MCA and by oxidation to glyoxylate. The sites and mechanism(s) for dehalogenation are uncertain. Glyoxylate and its catabolites are all naturally occurring endogenous molecules. Formation of glycine provides a route of entry of DCA into the general carbon pool of the host.

to the lowest dose in one subject led to normalization of transaminase levels. There is no clinical evidence that DCA is toxic to the eyes, kidneys, or gonads or induces neoplasia in any human tissue.

### Summary and Conclusions

Together, the results of these and other (5,7) investigations indicate that the kinetics and biotransformation of DCA are qualitatively similar when the chemical is administered to children or adults at therapeutically relevant doses, as depicted in Figure 6. DCA, and/or an intermediate, strongly inhibits its own metabolism, but the mechanism for this is unknown. Likewise, the quantitative significance of the putative pathways of its metabolism in any species remains to be determined, as do the early molecular events in the dehalogenation of DCA. The chemical appears to be relatively nontoxic when administered acutely and parenterally to healthy adults or to critically ill patients with acquired causes of lactic acidosis, but its long-term safety can be more adequately addressed by chronic treatment of children with CLA.

DCA is unique among chlorinated hydrocarbons in that research on its kinetics, metabolism, and toxicology has been driven by both environmental and therapeutic concerns. The interesting consequence is that much of the animal experimentation has been conducted using doses much closer to those used clinically than to levels to which human populations may be exposed, either by chlorination of municipal drinking water or by groundwater contamination as occurs, for example, at certain Superfund sites. Thus, very little animal and almost no human studies have examined the pharmacology or toxicology of DCA at environmentally relevant concentrations. Therefore, the appropriateness of extrapolating animal toxicology studies to humans in determining the health risk from DCA exposure is problematic thus far. In fact, this caveat may apply to the extrapolation of nonhuman toxicologic data generated for a number of chlorinated hydrocarbons, including precursors of DCA. In the case of DCA, however, its status as an investigational drug for both pediatric and adult diseases affords an invaluable opportunity to prospectively assess its chronic toxicity in humans.

### REFERENCES AND NOTES

1. Miller JW, Uden PC. Characterization of nonvolatile aqueous chlorination products of humic substances. *Environ Sci Technol* 17:150-157 (1983).
2. Uden PCC, Miller JW. Chlorinated acids and chloral in drinking water. *J Am Water Works Assoc* 75:524-527 (1983).
3. Mughal FH. Chlorination of drinking water and cancer: a review. *J Environ Pathol Toxicol Oncol* 11:287-292 (1992).
4. Jolley RL. Basic issues in water chlorination: a chemical perspective. In: *Water Chlorination: Chemistry, Environmental Impact and Health Effects*. Vol 5. Chelsea, MI: Lewis Publishers, 1985;19-38.
5. Stacpoole PW. The pharmacology of dichloroacetate. *Metabolism* 38:1124-1144 (1989).
6. Henderson GN, Yan Z, James MO, Davydova N, Stacpoole PW. Kinetics and metabolism of chloral hydrate in children: identification of dichloroacetate as a metabolite. *Biochem Biophys Res Commun* 235:695-698 (1997).
7. Stacpoole PW, Henderson, GN, Yan Z, Cornett R, James MO. Pharmacokinetics, metabolism and toxicology of dichloroacetate. *Drug Metab Rev* (in press).
8. Jackson VN, Halestrap AP. The kinetics, substrate, and inhibitor specificity of the monocarboxylate (lactate) transporter of rat

- liver cells determined using the fluorescent intracellular pH indicator, 2',7'-bis(carboxyethyl)-5(6)-carboxyfluorescein. *J Biol Chem* 271:861-868 (1996).
9. Bersin RM, Stacpoole PW. Dichloroacetate as metabolic therapy for myocardial ischemia and failure. *Am Heart J* 134:841-855 (1997).
  10. Chu P-I. Pharmacokinetics of Sodium Dichloroacetate. PhD dissertation. Gainesville, FL:University of Florida, 1987.
  11. Yan Z, Henderson GN, James MO, Stacpoole PW. Determination of dichloroacetate and its metabolites in human plasma by gas chromatography-mass spectrometry. *J Chromatography B* 703:75-84 (1997).
  12. Curry SH, Lorenz A, Chu P-I, Limacher M, Stacpoole PW. Disposition and pharmacodynamics of dichloroacetate (DCA) and oxalate following oral DCA doses. *Biopharm Drug Disp* 12:375-390 (1991).
  13. Stacpoole PW, Barnes CL, Hurbanis MD, Cannon SL, Kerr DS. Treatment of congenital lactic acidosis with dichloroacetate. *Arch Dis Child* 77:535-541 (1997).
  14. Stacpoole PW, Harman EM, Curry SH, Baumgartner TG, Misbin RI. Treatment of patients with lactic acidosis with dichloroacetate. *N Engl J Med* 309:390-396 (1983).
  15. Stacpoole P, Wright EC, Baumgartner TG, Misbin RI, Bersin RM, Buchalter S, Curry SH, Duncan C, Hackett R, Harman EM, et al. A controlled clinical trial of dichloroacetate treatment in patients with lactic acidosis. *N Engl J Med* 327:1564-1569 (1992).
  16. Curry SH, Chu P-I, Baumgartner TG, Stacpoole PW. Plasma concentrations and metabolic effects of intravenous sodium dichloroacetate. *Clin Pharmacol Ther* 37:89-93 (1985).
  17. Stacpoole PW. Unpublished observation.
  18. Stacpoole PW, Moore GW, Kornhauser DM. Metabolic effects of dichloroacetate in patients with diabetes mellitus and hyperlipoproteinemia. *N Engl J Med* 298:526-530 (1978).